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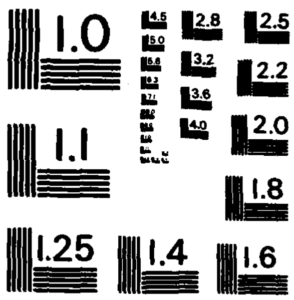

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A New Approach to Polymer Chemistry: Organometallic and Bioactive Phosphazenes

by

Harry R. Allcock

Prepared for Publication

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Journal of Polymer Science

The Pennsylvania State University
Department of Chemistry
University Park, Pennsylvania

December 5, 1983

Proceedings of Symposium on Polymers with Unusual Properties

A New Approach to Polymer Chemistry: Organometallic and Bioactive Phosphazenes

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Abstract: Polyphosphazenes are prepared by a substitutive process that involves nucleophilic displacement reactions on poly(dihalophosphazenes). A variety of strategies are described for the utilization of this approach for the preparation of polymeric drugs and polymer-bound transition metal systems.

Future Challenges in Polymer Synthesis

The main challenge in polymer synthesis during the past forty years has been the preparation of new materials with ever more sophisticated solid state properties. By this is meant the utilization of polymers for their solid state chain entanglement or chain packing attributes. This underlies the practical reasons for the use of polymers in fibers, films, elastomers, and as structural materials. Much remains to be done in this area, especially with respect to high strength, heat stable materials, or polymers with special surface properties. The synthesis of solid polymers that can conduct electricity has also received wide attention.

However, in recent years, it has become generally recognized that the solution properties of polymers and the detailed molecular arrangement of side groups along an isolated macromolecular chain hold important keys to the future development of polymer science. Prominent among the areas being investigated are the use of polymers as carrier molecules for bioactive agents (drugs, metalloporphyrins, enzymes, etc.), and as "immobilization carriers" for transition metal catalyst systems. The distant prospect that synthetic polymers may be prepared with precisely sequenced arrangements of different side groups for use as self-assembling structures, templates for the synthesis of complementary macromolecules, or even for information storage at the molecular level, remains an intriguing prospect.

In many cases the roadblock to achieving these breakthroughs lies in the limitations of presently available synthetic methods.

Substitution Reactions on High Polymers

Most modern synthetic macromolecules are synthesized by the polymerization of organic monomers, with the use of the well-known addition-, condensation-, or ring-opening-polymerization methods. However, there exists an alternative approach to polymer synthesis which involves the substitutive transformation of preformed high polymers. In this method reactive side groups attached to a polymer chain are replaced by other groups with an attendant change in the physical and chemical properties of the macromolecule.

This method is intuitively appealing because it avoids the usual problems involved in chain-building from new monomers or the need to search for appropriate polymerization initiators or reaction conditions. Once the backbone has been constructed the task of new polymer synthesis simplifies to a study of substitution reactions. In addition, the use of neighboring group polar effects, steric and electronic effects, and sequential substitution processes offers the prospect that quite sophisticated macromolecular structures might be constructed by this approach.

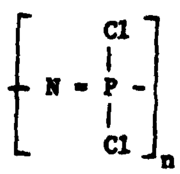
A number of well-known polymers are, in fact, prepared by this techique. The hydrolysis of poly(vinyl acetate) to poly(vinyl alcohol) or the nitration or acetylation of cellulose are obvious examples. Yet, given the enormous opportunities of modern substitutive chemistry, this approach accounts for only a trivial fraction of the polymer syntheses employed today. It is worthwhile to ask why.

Substitution reactions carried out on small molecules can generally be accomplished with ease because the overall efficiency of substitution is only a secondary consideration. If 75% of the small molecules in a reaction mixture are transformed, the remaining 25% are discarded or recovered, and the yield of product is acceptable. But if only 75% of the side groups along a polymer chain can be replaced by other groups, the yield of the fully substituted product is zero. Thus, different considerations govern chemistry carried out on large, linear molecules from those with which most chemists are familiar. High reactivity of the polymeric substrate is the key to polymer synthesis by the macromolecular substitution route.

Moreover, it is essential that substitution reactions carried out on high polymers should be free from side reactions that may result in main chain cleavage or crosslinking. A crosslinked, partly-substituted polymer would be an unsatisfactory substrate for replacement of the remaining side groups.

Poly(dihalophosphazenes) as Reaction Substrates

Very few organic macromolecules have the necessary high reactivity to function as substrates for efficient substitution reactions. It was recognized a number of years ago[1-3] that such reactivity might be found among certain inorganic macromolecules, especially those based on the halophosphazene structures 1 and 2.



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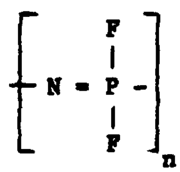

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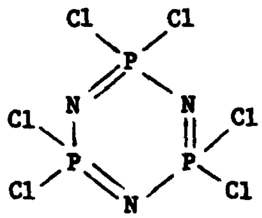
(n ≈ 15,000
MW ≈ $2 \cdot 10^6$)

Enough evidence exists about the reactivities of small molecules, such as PCl_3, PCl_5, or small-molecule analogues of 1 or 2, such as the cyclic $(NPCl_2)_3$ (3), $(NPCl_2)_4$ (4), or $(NPF_2)_3$ (5), to suggest that the phosphorus-halogen bond is highly reactive toward cleavage by organic nucleophiles.



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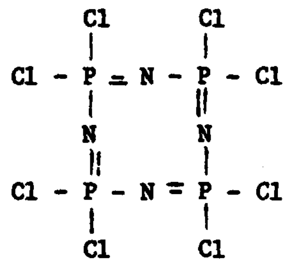

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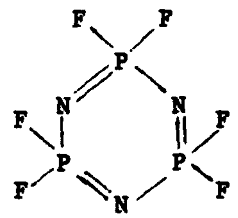

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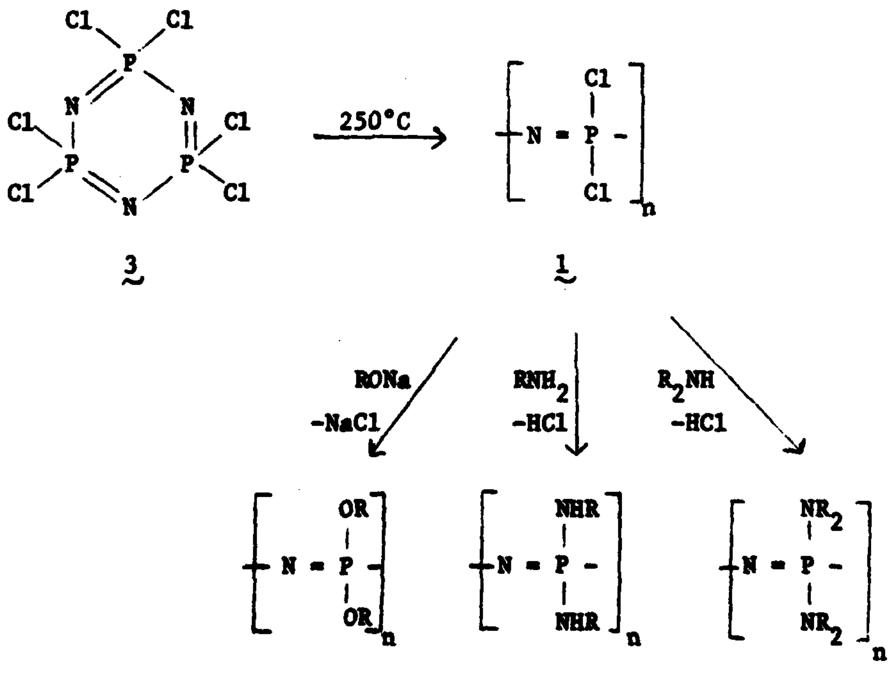
Our initial problem was to develop methods for the synthesis of uncrosslinked forms of 1 and 2.[1,2,4] It was then possible to demonstrate that 1 and 2 are reactive substrates for reactions with organic nucleophiles.[1-4] Under suitable conditions all the halogen atoms can be replaced.[1-9] This approach is summarized in Scheme I.



6 7 8

Scheme I n ≈ 15,000

It should be noted that a close correspondence exists between the reactions of polymers such as 1 and 2, and cyclic oligomers such as 3-5.[10] Hence, the oligomers can be used as models for exploratory reactions that are later applied to the high polymers.

A serious challenge at present is to extend the reactions shown in Scheme I to those in which poly(dihalophosphazenes) react with Grignard-, organolithium-, or organocopper reagents as the route to the synthesis of polyphosphazenes with alkyl- or aryl groups linked directly to phosphorus.[11]

Bioactive Polyphosphazenes

It is widely believed that the effectiveness of chemotherapeutic drugs can be improved by targeting them to specific sites in the body and by providing for a controlled release of the drug to maintain optimum concentration. In principle, this can be achieved by the attachment of chemotherapeutic agents to polymer molecules. The carrier polymer must meet certain requirements. First, it should preferably be soluble in aqueous media at pH 7. Second, it should be degradable to non-toxic small molecules that can be excreted or metabolized. And third, ideally, it should carry a "homing" unit that maximizes the concentration of the polymer-drug combine at the site within the organism where chemotherapy is needed.

A few polyphosphazenes have been found to undergo hydrolytic degradation in aqueous media. These are polymers that bear amino acid ester[12] or imidazolyl side groups.[13] Water-soluble polymers that bear glucose side groups have also been synthesized.[14]

The following methods have been developed recently for the attachment of bioactive cosubstituent groups to a polyphosphazene chain:

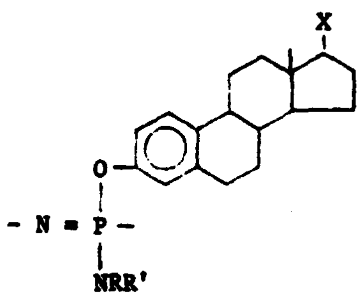
(1) Steroidal side groups can be attached by reaction of an alkali metal 3-steroidoxide with poly(dichlorophosphazene).[15] Unreacted chlorine atoms are then removed by treatment with an amino acid ester or amine. A typical structure is illustrated in 9.

(2) Bioactive amines react directly with poly(dichlorophosphazene).[16] Typical amines include procaine, benzocaine, and chloroprocaine. These are anesthetic or antirrhythmic agents. Structure 10 is illustrative of this mode of linkage.

(3) Biologically active amines have also been linked to aryloxyphosphazenes by Schiff's base formation through a pendent aldehydic group. Drugs such as sulfadiazine have been coupled in this way (11).[17]

(4) An active carboxylic acid, such as nicotinic acid or N-acetylpenicillamine, can be linked to an aminomethylene-aryloxyphosphazene by DCC-induced peptide coupling techniques to give structures such as 12.[18]

(5) Finally, the anticoagulent, heparin, has been coupled to a quaternized aryloxyphosphazene, as shown in 13.[19]



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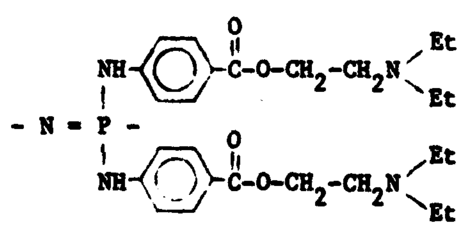

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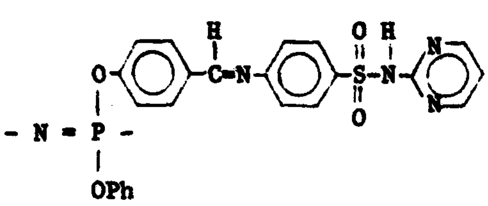

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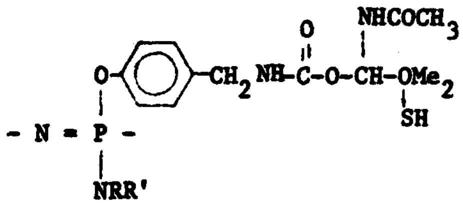

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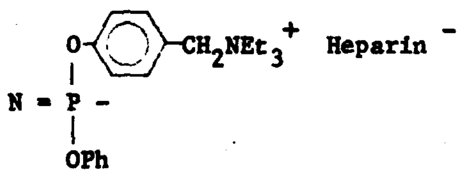

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Organometallic Phosphazenes

Polymer-bound transition metal systems are of interest as catalyst systems and possibly as electroactive materials. We are currently developing methods by which transition metal organometallic groups can be linked to a polyphosphazene chain. Methods explored to date include the following:

(1) The backbone nitrogen atoms of polyphosphazenes are quite basic provided that electron-supplying side groups are attached to each skeletal phosphorus atom. Such polymers bond metals strongly by coordination of the skeletal nitrogen atoms to the metal.[20]

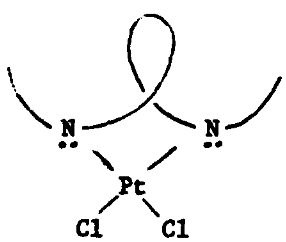
(2) Aryloxyphosphazene high polymers that bear phosphine units on the aromatic rings coordinate to AuCl, $H_2Os_3(CO)_{10}$, $Mn(CO)_2(C_5H_5)$, RhCl(CO), and $Fe(CO)_3$ units. Di-coordinative crosslinking can take place with the rhodium and iron systems.[21]

(3) Pendent acetylenic units attached to a phosphazene skeleton form π-bonding sites for organometallic units such as $Co_2(CO)_6$.[22]

(4) Pendent nido-carboranyl groups bind to transition metal units such as $Rh(Ph_3)_2H$ groups to form polymer-bound catalytic systems. The organometallic unit retains its activity as an olefin hydrogenation catalyst.[23]

(5) Finally, halophosphazenes react with organometallic anions to yield species with direct phosphorus-metal bonds.[24] This work is currently at the model compound level and is being extended to the high polymers.

These structures are illustrated in 14-18.



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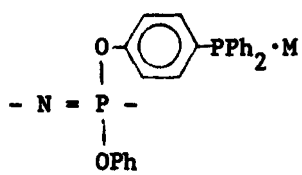

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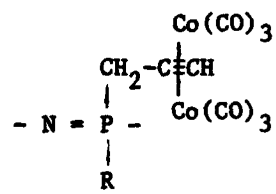

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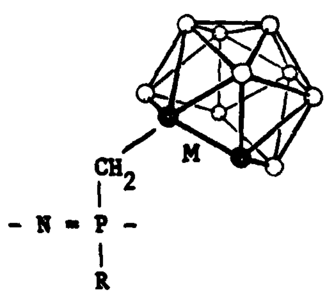

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References

1. Allcock, H. R.; Kugel, R. L. J. Am. Chem. Soc. 1965, 87, 4216.

2. Allcock, H. R.; Kugel, R. L.; Valan, K. J. Inorg. Chem. 1966, 5, 1709.

3. Allcock, H. R.; Kugel, R. L. Inorg. Chem. 1966, 5, 1716.

4. Allcock, H. R.; Patterson, D. B.; Evans, T. L. Macromolecules. 1979, 12, 172.

5. Allcock, H. R.; Cook, W. J.; Mack, D. P. Inorg. Chem. 1972, 11, 2584.

6. Singler, R. E.; Schneider, N. S.; Hagnauer, G. L. Polym. Eng. Sci. 1975, 15, 322.

7. Singler, R. E.; Hagnauer, G. L. "Organometallic Polymers" (Carraher, C. E.; Sheats, J. E.; Pittman, C. U., Eds.), Academic Press: New York, 1978, p. 257.

8. Schneider, N. S.; Desper, C. R.; Singler, R. E.; Alexander, M. N.; Sagalyn, P. L., ibid, p. 271.

9. Tate, D. P. J. Polym. Sci., Symp. 48. 1974, 48, 33.

10. Allcock, H. R. Accts. Chem. Res. 1979, 12, 351.

11. Allcock, H. R.; Patterson, D. B.; Evans, T. L. J. Am. Chem. Soc. 1977, 99, 6095.

12. Allcock, H. R.; Fuller, T. J.; Mack, D. P.; Matsumura, K., Smeltz, K. M. Macromolecules. 1977, 10, 824.

13. Allcock, H. R.; Fuller, T. J. J. Am. Chem. Soc. 1981, 103, 2250.

14. Allcock, H. R.; Scopelianos, A. G. Macromolecules. submitted.

15. Allcock, H. R.; Fuller, T. J. Macromolecules. 1980, 13, 1338.

16. Allcock, H. R.; Austin, P. E.; Neenan, T. X. Macromolecules. 1982, 15, 689.

17. Allcock, H. R.; Austin, P. E. Macromolecules. 1981, 14, 1616.

18. Allcock, H. R.; Neenan, T. X.; Kossa, W. C. Macromolecules. 1982, 15, 693.

19. Neenan, T. X.; Allcock, H. R. Biomaterials. 1982, 3, 78.

20. Allcock, H. R.; Allen, R. W.; O'Brien, J. P. J. Am. Chem. Soc. 1977, 99, 3984.

21. Allcock, H. R.; Lavin, K. D.; Tollefson, N. M. unpublished work.

22. Allcock, H. R.; Nissan, R. A.; Whittle, R. R. unpublished work.

23. Allcock, H. R.; Scopelianos, A. G.; Whittle, R. R.; Tollefson, N. M. J. Am. Chem. Soc., in press.

24. Allcock, H. R.; Greigger, P. P.; Wagner, L. J.; Bernheim, M. Y. Inorg. Chem. 1981, 20, 716.

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